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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/171,854	10/22/98	JOOS	S 3528.38.US00

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EXAMINER	
SISSON, B	
ART UNIT	PAPER NUMBER
1655	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/171,854	Applicant(s) JOOS et al.	
	Examiner Bradley L. Sisson	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8* is/are rejected.

7)☒ Claim(s) *6 and 7* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 1990* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Specification

1. Acknowledgement is made of applicant having filed a substitute specification on even date with the filing of the subject application. The cover page to the substitute specification makes references to changes in the text; however, it is not clear just where the changes have been made. No markedup copy of the specification has been found. Accordingly, the substitute specification has NOT been entered. In the event that applicant does wish to have a substitute specification entered, a markedup copy of the substitute specification needs to be filed and a request for the substitute specification be made.

2. The disclosure is objected to because of the following informalities: The disclosure has been found to contain a representation of a nucleotide residue sequence for an oligonucleotide which is not accompanied with the requisite SEQ ID NO.

Appropriate correction is required.

Drawings

3. The drawings remain objected to for reasons of record; see the PTO-948 that was attached to Paper No. 6. Acknowledgement is made of applicant's willingness to file corrected drawings upon notification of allowable subject matter.

Claim Objections

4. Claims 6 and 7 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the presence of over representations of chromosomal segments in a population of immortalized cells derived from a cell line, does not reasonably provide enablement for the detection and determination of any type of "change" in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success.

The Amount of Direction or Guidance Provided and The Presence or Absence of Working Examples

The specification has been found to provide but one example (pages 5-14). This sole example details the use of Colo 320(HSR) cells. Specifically, the cells were stopped at interphase. Separately, "normal" DNA was modified such that it was end-labeled by DOP PCR. This normal DNA was further modified such that it had a size range of from about 500 to 1000 base pairs in length. The size-selected and tagged normal DNA was then used in an *in situ* hybridization where the target was the nuclei of Colo 320 (HSR) cells that had been arrested at interphase. Subsequent to performing *in situ* hybridization, nuclei were selectively removed from a slide by use of a needle and placed into a vial so to be subjected to DOP PCR. The specification teaches that applicant was able to identify between 89% and 94% of all chromosomal over-representations as opposed to 38% to 44% without the Tagged Genome Hybridization (TGH) process.

The specification is essentially silent as to the detection of any other change in DNA. While the specification was able to detect "over-representations," the specification has not shown that any of the "over-representations" have been correlated with any particular condition or trait.

The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art

The state of the PCR art is fairly well developed. However, the application of PCR to the detection of specific sequences has been predicated upon the use of primers that are specific for a particular target sequences. In the present case, however, the method entails the use of the complete genome of "normal" cells. Given that there are silent mutations in the genome of most individuals, it is not readily apparent just what constitutes "normal." Setting this issue of indefiniteness aside, the state of the art is relatively undeveloped as to how the use of complete genomes for priming/hybridization will result in the accurate detection of any change in a genome.

The Relative Skill of Those in the Art

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

The Breadth of Scope of the Claims

The claims have sufficient breadth of scope so to encompass the detection of any change, no matter how slight, in any genomic material from a cell. It is noted further that the target cell may be isolated or in a highly heterogeneous mixture.

For the above reasons, and in the absence of convincing evidence to the contrary, applicant is urged to consider narrowing the scope of the claims to those embodiments adequately supported by the disclosure.

6. Claims 1-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As presently worded the method of claims 1-5, and the kit of claim 8, relate to the detection of any change in the DNA of any cell or combination of cells. The specification, however, has been found to support the detection of changes in chromosomal number, but not the detection of any change in the DNA. It is noted with particularity that there can be any number of changes in a chromosome without there being any change in chromosomal number. Accordingly, the amendment to claims 1 and 8 has been found to introduce new matter into the claims. Applicant is urged to consider rewording the claims such that they are more closely drawn to the originally presented inventions.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite with respect to just what constitutes "normal cells." It is noted that the claimed method is to result in the detection of any change in a cell. Given that "normal" cells are considered to have silent mutations, e.g., single nucleotide polymorphisms, it is not clear how such mutations are to be considered in respect to the cell being "normal" as compared to a cell that is considered to be not normal. Claims 2-5 and 8, which depend from claim 1, fail to overcome this issue and are similarly indefinite.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Worton et al., in view of Batt et al.

Worton et al., column 13, discloses the development and use of nucleic acid sequences that are derived from both normal and mutated sequences. The sequences can be obtained from having performed a primer extension reaction. Worton et al., do not teach explicitly of the primers/probes being tagged or labeled.

Batt et al., column 10, discloses that the primers may be labeled or tagged.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the aspect of labeling or tagging primers or primer extension products as such would have enabled the ordinary artisan to have detected the presence of the sequence, be it normal or mutated, and to have placed such reagents into a kit format for the obvious expediency of convenience.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1655

BLS
May 7, 2001